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New Thinking Needed for an Age-Old Disease

Leading Alzheimer's scientist calls for a change in direction by focusing on Tau tangles to halt or slow disease progression

BOSTON, 7 November 2012 – Speaking at the CNS Leaders' Forum today in Boston, Dr. Claude Wischik, MD, PhD, Professor of Old Age Psychiatry at the University of Aberdeen, Scotland and Executive Chairman and Co-founder of TauRx Therapeutics Ltd., called for a change in direction in the quest to find a disease-modifying treatment that can effectively halt progression of Alzheimer's, one of the most challenging global health issues today.

Having conducted an analysis based on published survival data, Professor Wischik noted that the underlying pathology of Alzheimer's known as Tau tangles is present in the brain up to 30 years before clinical symptoms develop and that the presence of this pathology is highly correlated with disease progression. These insights run contrary to the direction of pharmaceutical industry research and drug development over the last 20 years which has centred on the presence of amyloid plaques as the pivotal cause of Alzheimer's progression. Such approaches based on the 'amyloid theory' have not yet been proven successful to date.

The survival analysis conducted by Professor Wischik and colleagues at TauRx was based on data from the Braak group in Frankfurt (Ohm et al., 1995), which examined the brains of 847 cases coming to post-mortem ranging in age from 45 to 95. "There was an average of 17 cases per year of life in this series, making it the largest and most authoritative study of its kind," he said.

The Braak staging system, established in 1991 by German Professor Heiko Braak and colleagues (Braak and Braak, 1991), divides the very characteristic pattern of spread of Tau tangles in the brain into 6 stages. These tangles first appear in the part of the brain responsible for learning, short-term memory, thinking and planning (stages 1 and 2), spread through the hippocampus, responsible for spatial awareness and navigation and for consolidation of memory (stages 3 and 4) and finally reach the areas that affect the ability to communicate, recognize family and loved ones and to care for oneself (stages 5 and 6). Dementia becomes apparent clinically at Braak stages 3 to 4. According to Professor Wischik,

there are many studies in the field, including those from his own group, repeatedly showing the strong correlation between the gradual but relentless spread of these tangles through the brain and the equally gradual but relentless increase in dementia in patients with Alzheimer's disease. In contrast, there is not such strong correlation between the presence of amyloid plaques and dementia.

Using the data from Braak's large post-mortem series, the TauRx group applied actuarial survival analysis techniques to calculate the probability Braak stage transitions by age. They then applied these probabilities to WHO US population figures for 2010. Their conclusions contradict the "beta-amyloid early, Tau-tangle late" hypothesis. There is a simple linear correlation between age and likelihood of entering the Braak sequence that begins at age 35 and reaches 100% by age 85. Stage 2 starts at about age 48 and peaks at age 63. Stage 3 starts at about 53 and peaks in the range 63 – 73 years. Stages 4 – 6 start at age 58 and peak at the age of 88. "This indicates that there is a very long pre-clinical interval of about 30 years between the start of the process and reaching the earliest stages of measurable loss of cognitive function," said Professor Wischik.

"The fundamental problem with the Amyloid mainstream view is that it assumes, without any clear evidence, that a defect in the Amyloid processing pathway is the only rate-limiting trigger for the Tau aggregation cascade," he said. "However, if changes in the Amyloid pathway represent only one of the possible accelerators for the Tau aggregation pathway, then even early intervention focussed on Amyloid may serve only to delay the inevitable. The fact that the clinical efficacy seen in the latest Amyloid trials is modest, in fact no better than currently available symptomatic treatments, suggests that the impact of Amyloid therapies, even if finally proven by generally accepted regulatory standards, will remain modest."

In his presentation, Professor Wischik noted that given these insights and recent failures of several amyloid-targeted investigational approaches, "there is no better time than now to focus our attention on 'The Other Pathology' – the tangles of Tau protein. That is why we have initiated our Phase 3 program with our Tau Aggregation Inhibitor, LMTX™ to test whether we can replicate our Phase 2 results showing arrest of disease progression with a treatment that blocks the Tau aggregation pathway."

He continued, "Azheimer's has the potential to become this mostly costly medical condition for all nations. Healthcare spending on this disease are forecast to balloon in the next twenty years."Prof. Wischik urgently calls for industry and academia to switch research focus to understanding more about the process behind the initial triggering of the toxic aggregation of Tau protein that ultimately leads to the release of Tau tangles from dead neurons. "This change in direction *must* occur if we are ultimately to defeat this horrifying disease."

About Professor Claude Wischik:

Professor Calude Wischik is co founder and chairman of TauRx Therapeutics and professor of Old Age Psychiatry at the University of Aberdeen, Scotland. A pioneer in Tau research, Prof. Wischik's work on Tau pathology began in 1985 in the laboratory of Sir Martin Roth, who was the first to correlate tangles with Alzheimer's dementia, and later with Sir Aaron Klug (Nobel Laureate) at Cambridge University. Prof. Wischik subsequently discovered the Tau protein compositional structure of the Alzheimer tangles and established that it was possible to dissolve tangles with pharmaceutically viable compounds that act as Tau Aggregation Inhibitors. He also demonstrated a direct link between clinical dementia and Tau aggregation at the biochemical level, irrespective of ß-amyloid load in human brain. As TauRx Chairman, Prof. Wischik has led the company to its present stage, has developed its portfolio of projects to the phase 3 clinical level and has worked with his Singaporean colleagues to raise over $300m to date.

About TauRx Therapeutics:

TauRx Therapeutics Ltd was established in Singapore in 2002 with the aim of developing new treatments and diagnostics for a range of neurodegenerative diseases based on an entirely new approach which targets aggregates of abnormal fibres of Tau protein that form inside nerve cells in the brain. The TauRx team have since discovered that LMTX™ could also have beneficial effects in several other neurodegenerative diseases associated with Tau pathology, as well as other protein aggregation disorders including Progressive Supranuclear Palsy, Parkinson's, Huntington's and Frontotemporol Dementia [FTD-Pick's Disease].

TauRx announced on October 30th the initiation of two Phase 3 clinical studies involving over 1,000 Alzheimer's patients; the studies will examine the safety and effectiveness of the company's LMTX™ drug in reducing the rate of decline in cognitive function in these patients. Encouraging results in a substantial Phase 2 study, supported by preclinical data indicating that the drug may be able to dissolve aggregations of Tau protein before they become tangles, have resulted in the company being given the green light by regulators in both the US and EU to proceed into Phase 3.

TauRx headquarters are in Singapore and its primary research facilities are in Aberdeen, Scotland.

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